Risk of Developing Pyoderma Gangrenosum after Procedures in Patients with a Known History of Pyoderma Gangrenosum – A Retrospective Analysis

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Title: Risk of Developing Pyoderma Gangrenosum after Procedures in Patients with a Known History of Pyoderma Gangrenosum – A Retrospective Analysis

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Abstract

Background: The risk of postoperative pyoderma gangrenosum (PG) in patients with a known history of PG is unknown.

Objective: To quantify risk and identify patient/procedure-related risk factors for postsurgical PG recurrence/exacerbation in patients with known history of PG.

Methods: We retrospectively evaluated the likelihood of postsurgical PG recurrence/exacerbation for all patients with a confirmed diagnosis of PG at Brigham & Women's Hospital and Massachusetts General Hospital from 2000-2015.

Results: 5.5% (n=33) of procedures led to recurrence of PG in 15.1% (n=25) of patients. Compared to skin biopsy, small open surgeries had an adjusted odds ratio (aOR) of 8.65 (1.55, 48.33) for PG recurrence/exacerbation; large open surgeries had an aOR of 5.97 (1.70, 21.00); and Mohs surgery/skin excision had an aOR of 6.47 (1.77, 23.61). PG chronically present at the time of procedure had an aOR of 4.58 (1.72, 12.22). Immunosuppression, time elapsed since original PG diagnosis, and procedure location did not significantly influence risk.

Limitations: Our study is limited by its retrospective nature and relatively small sample size.

Conclusion: There is a small but clinically meaningful risk of postsurgical PG recurrence/exacerbation in patients with known history of PG; higher risks occur with more invasive procedures and chronically present PG.

Keywords: Pyoderma gangrenosum, pathergy, risk factors, postoperative, recurrence, exacerbation, prophylaxis

Capsule Summary

- The risk of postoperative pyoderma gangrenosum (PG) in patients with history of PG is unknown.
- 15.1% of patients experienced postsurgical PG recurrence/exacerbation; risk increased with more invasive procedures and chronic PG at the time of the procedure.
- There is a small but clinically meaningful risk of postsurgical PG in patients with a known history of PG.

Introduction

Pyoderma gangrenosum (PG) is a neutrophilic process characterized by pathergy.[1] Postoperative PG as a primary phenomenon has been characterized in the literature as being less likely associated with systemic diseases, with onset usually in the first week after the procedure is performed. [2,3]

Little is known about the risk for postoperative PG or recurrence/exacerbation of PG in patients with a known history of PG. Quantifying overall and procedure-specific risks for postoperative PG recurrence/exacerbation may affect medical decision making for patients with known history of PG, such as initiating prophylactic immunosuppression prior to procedures or avoiding/adjusting the timing of elective procedures. In this study, we aim to evaluate the risk for PG recurrence or exacerbation after different types of procedures in patients with a known history of PG.

Methods

We searched the Research Patient Data Repository, a database of the medical records of all patients seen at Partners Healthcare, for patients with PG who underwent procedures at the Brigham & Women's Hospital and Massachusetts General Hospital from 2000-2015 using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code (686.01) for pyoderma gangrenosum. Medical records of returned cases were individually reviewed to confirm a diagnosis of PG using previously described major and minor criteria suggestive of PG diagnosis.[4] Relevant information regarding the original PG and all subsequent

surgical procedures underwent by the patient since the original PG diagnosis were extracted, with the primary outcome being PG exacerbation or recurrence within 30 days of the procedure. All data were managed using REDCap (Research Electronic Data Capture).[5] Patients without a diagnosis of PG, subsequent procedures, or adequate clinical documentation were excluded.

The types of procedures examined were 1) skin biopsies, 2) minimally invasive surgeries/small needle injections such as laparoscopies, arthroscopies, core-needle biopsies, and epidural injections, 3) small open surgeries such as thyroid surgeries and lumpectomies, 4) large open surgeries such as exploratory laparotomies and colectomies, and 5) Mohs surgery/skin excision and debridement (Supplementary Table 1). Chronically present PG at the time of surgery was defined as PG present for >1 year at the time of surgery or per clinician documentation.

Procedure-level and patient-level PG recurrence rates were presented for patient demographics and clinical characteristics. Univariable and multivariable analysis was performed using logistic regression mixed models. Random intercepts were included in the regression models to account for possible within-person correlation for patients with multiple additional procedures. Variables with $p<0.10$ from the univariable analysis were included in the multivariable regression model. Adjusted and unadjusted odds ratios were calculated. All analyses were performed using SAS 9.4 (Cary, NC). This study was approved by the Partners Healthcare Institutional Review Board.

Results

Of the 530 patients identified using ICD-9-CM codes for PG, 166 patients met inclusion criteria with a confirmed diagnosis of PG and subsequent procedures. Each patient underwent a median of 2 (interquartile range 1, 4) additional surgeries, for a total of 601 surgeries evaluated. The mean age was 52.8 years, and 80.1% (n=133) were women. The most common PG related comorbidity was inflammatory bowel disease (44.6%, n=74), and the most common location of original PG was on the lower extremities (57.8%, n=96) (Table 1).

We found a total of 33 cases of postsurgical PG exacerbation/recurrence, occurring in 25 patients, accounting for a recurrence rate of 5.5% (33/601) by procedure (Table 2) and 15.1% (25/166) by patient. Univariable analysis at the procedure level demonstrated that the exacerbation/recurrence rate was significantly associated with procedure type ($p=0.022$) and having chronically present PG at the time of procedure ($p=0.041$) (Table 2). Age ≥ 60 at time of surgery, sex, comorbidities, location of the original PG/surgery, location of surgery being at the same site as original PG, new/expanding/multifocal PG at the time of procedure, chronic or prophylactic immunosuppression were not statistically significant predictors of PG recurrence. Furthermore, time elapsed since the original PG and the additional surgery also were not associated with recurrence.

Multivariable regression modeled exacerbation/recurrence as a function of age at time of surgery, chronically present PG, and procedure types ($p<0.10$). Age ≥ 60 at time of surgery was associated with increased odds of PG recurrence and was of marginal statistical significance with an adjusted odds ratio (aOR) of 2.41 (95% CI: 0.92, 6.39). Compared to risk of recurrence after skin biopsies, minimally invasive surgeries/small needle injections had similar risk for PG

recurrence with an aOR of 0.96 (95% CI: 0.16-5.60). Other procedure types were associated with increased odds of recurrence, with an aOR of 8.65 (95% CI: 1.55-48.33) for small open surgeries, an aOR of 5.97 (95% CI: 1.70-21.00) for large open surgeries, and an aOR of 6.47 (95% CI: 1.77-23.61) for Mohs surgery/skin excision (Table 3). Chronically present PG at the time of surgery had an aOR of 4.58 (95% CI: 1.72-12.22).

In a sensitivity analysis, we examined the relationship between patient-level characteristics at the time of first surgery with recurrence/exacerbation (n=166); age, gender, comorbidities, location of PG, multifocal ulcer, and chronic immunosuppression were not significantly associated with recurrence in this study.

Discussion

While pathergy associated with PG is a well-known phenomenon, our study found that the risk of postsurgical PG recurrence or exacerbation in patients with known history of PG is relatively low at 5.5% (33/601 surgeries). However, recurrence/exacerbation occurred in 15.1% (25/166 patients) of our patients, suggesting that the per-patient risk for experiencing a recurrence of postsurgical PG recurrence/exacerbation is clinically relevant. Independent risk factors influencing PG recurrence/exacerbation post-procedure were procedure type and having chronic PG at the time of procedure. More invasive procedures such as small and large open surgeries, Mohs surgery/skin excision and debridement were more likely to be associated with PG recurrence.

This study builds on existing literature in PG by quantifying the risk of postsurgical PG recurrence/exacerbation in patients with known history of PG, which will help inform patients and physicians when assessing the risk of surgical procedures. In general, the greater the amount of tissue manipulation, the higher the likelihood of subsequent PG. This concept has face validity and is consistent with the current understanding of the pathophysiology of PG and pathergy, which is thought to involve dysfunction and up-regulation of neutrophil activities.[6,7] Invasive surgeries are likely associated with more tissue manipulation, inflammation and surgical stress. Time elapsed between the original PG diagnosis and surgery, did not significantly influence recurrence risk, suggesting that the neutrophilic dysfunction of PG may be intrinsic to the host with limited change over time.

Chronic or prophylactic immunosuppression leading up to surgery did not significantly influence recurrence risk in our study. However, this finding may reflect confounding by indication in that the use of chronic immunosuppression may be correlated with baseline severity of original PG, which was not a variable that we could account for due to lack of standardized clinical assessments. As such, further studies are needed to evaluate the current practice or efficacy of prophylactic immunosuppression prior to procedures in patients with history of PG.

While we identified independent predictors of recurrence risk on a procedure level, we did not find clinical factors that significantly predicted risk at the patient level. Smaller sample size on a per patient basis (25 patients with PG recurrences vs. 33 procedures complicated by PG recurrence) may have limited our ability to detect significant factors.

The results of this study must be interpreted in the context of our study design. Recurrent PG is rare, thereby limiting our ability to detect differences in recurrence risk between small open, large open, and Mohs surgery/skin excision procedures. The small sample sizes may also limit our detection of significance when examining risk factors at the patient level as discussed above. Future studies should confirm our findings in larger, multi-centered, prospective trials, especially evaluating whether risk factors identified in our study can be modified to decrease the risk of postsurgical PG recurrence/exacerbation.

Conclusion:

We conclude that there exists a small but clinically meaningful risk of postsurgical PG recurrence/exacerbation in patients with a known history of PG, with higher risks seen with more invasive procedures and in patients with chronically present PG at the time of surgery. Time elapsed between the original PG diagnosis, and surgery and prophylactic immunosuppression did not significantly affect the rate of PG recurrence.

References

1. Binus AM, Qureshi AA, Li VW, Winterfield LS. Pyoderma gangrenosum: a retrospective review of patient characteristics, comorbidities and therapy in 103 patients. *The British journal of dermatology*. Dec 2011;165(6):1244-1250.

2. Tolkachjov SN, Fahy AS, Cerci FB, Wetter DA, Cha SS, Camilleri MJ. Postoperative Pyoderma Gangrenosum: A Clinical Review of Published Cases. *Mayo Clinic proceedings.* Sep 2016;91(9):1267-1279.

3. Tolkachjov SN, Fahy AS, Wetter DA, et al. Postoperative pyoderma gangrenosum (PG): the Mayo Clinic experience of 20 years from 1994 through 2014. *Journal of the American Academy of Dermatology*. Oct 2015;73(4):615-622.

4. Su WP, Davis MD, Weenig RH, Powell FC, Perry HO. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. *International journal of dermatology*. Nov 2004;43(11):790-800.

5. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.

6. Braswell SF, Kostopoulos TC, Ortega-Loayza AG. Pathophysiology of pyoderma gangrenosum (PG): an updated review. *Journal of the American Academy of Dermatology.* Oct 2015;73(4):691-698.

7. Alavi A, French LE, Davis MD, Brassard A, Kirsner RS. Pyoderma Gangrenosum: An Update on Pathophysiology, Diagnosis and Treatment. *American journal of clinical dermatology.* Jun 2017;18(3):355-372.

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264 Table 1: Patient characteristics

n (%)	Overall n=166
Age at PG diagnosis	
< 60	97 (58.4)
≥ 60	69 (41.6)
Gender	
Male	33 (19.9)
Female	133 (80.1)
Comorbidities	
Ulcerative colitis, Crohn's disease	74 (44.6)
Hematologic disorder	22 (13.3)
Solid malignancy	16 (9.6)
Arthritis	46 (27.7)
Psoriasis	14 (8.4)
Diabetes	28 (16.9)
PVD	15 (9.0)
No relevant comorbidities	23 (13.9)
Other (pertaining to PG)	16 (9.6)
Location of original PG	
Head/neck	10 (6.0)
Trunk	65 (39.2)
Upper extremities	16 (9.6)
Groin/genitals	12 (7.2)
Lower extremities	96 (57.8)
Number of additional surgeries	
1	52 (31.3)
2-3	56 (33.7)
≥ 4	58 (34.9)

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266 For results section:

267 mean (SD) age: 52.8 (17.6)

268 median (interquartile range) additional surgeries: 2 (1, 4)

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272 Table 2: Characteristics of additional surgeries and recurrence

	No. surgeries	n (%) with recurrences	p-value
Overall	601	33 (5.5)	
Age ≥ 60 at surgery	269	21 (7.8)	0.063
Female	485	27 (5.6)	0.927
Comorbidities			
Ulcerative colitis, Crohn's disease	322	14 (4.3)	0.317
Hematologic disorder	69	2 (2.9)	0.351
Solid malignancy	72	3 (4.2)	0.536
Arthritis	252	11 (4.4)	0.499
Psoriasis	66	5 (7.6)	0.469
Diabetes	115	10 (8.7)	0.173
PVD	58	1 (1.7)	0.239
No relevant comorbidities	68	5 (7.4)	0.551
Other (pertaining to PG)	46	3 (6.5)	0.698
Location of original PG (may be more than one)			
Head/neck	44	0 (0.0)	--
Trunk	246	16 (6.5)	0.441
Upper extremities	53	4 (7.5)	0.439
Groin/genitals	32	0 (0.0)	--
Lower extremities	351	17 (4.8)	0.385
Time between original diagnosis and additional surgery			
< 1 year	184	11 (6.0)	0.765
1-2 years	125	6 (4.8)	
≥ 2 years	292	16 (5.5)	
Location of additional surgery			
Head/neck	76	2 (2.6)	0.755
Trunk	250	12 (4.8)	
Upper extremities	44	3 (6.8)	
Groin/genitals	86	5 (5.8)	
Lower extremities	145	11 (7.6)	
Additional surgery in same location as original PG	180	8 (4.4)	0.318
Multifocal ulcer at time of diagnosis	246	16 (6.5)	0.350
Procedure type			
Skin biopsy	209	6 (2.9)	0.022
Minimally invasive surgeries / small needle injections*	116	2 (1.7)	
Small open surgeries	43	4 (9.3)	
Large open surgeries	129	10 (7.8)	
Mohs surgery / skin excision	104	11 (10.6)	
Chronic immunosuppression	313	15 (4.8)	0.637
Started immunosuppression for procedure	5	1 (20.0)	0.216
Chronically present PG at time of procedure	173	15 (8.7)	0.041

New/expanding PG at time of procedure	48	5 (10.4)	0.172

*includes: cardiac catheterization, laparoscopy, arthroscopy, thoracoscopy, core needle biopsy, epidural or other small needle injection;

p-values from generalized linear mixed models with random intercepts for patients with multiple additional procedures, binomial distribution and logit link

Table 3: Odds ratios for associations between patient and procedure characteristics and recurrence

	Unadjusted Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)
Overall		
Age ≥ 60 at surgery	2.31 (0.96, 5.56)	2.41 (0.92, 6.39)
Procedure type		
Skin biopsy	1 (Reference)	1 (Reference)
Minimally invasive surgeries / small needle injections*	0.62 (0.11, 3.50)	0.96 (0.16, 5.60)
Small open surgeries	3.34 (0.66, 16.88)	8.65 (1.55, 48.33) †
Large open surgeries	3.57 (1.08, 11.84) †	5.97 (1.70, 21.00) ‡
Mohs surgery/skin excision	5.92 (1.71, 20.44) ‡	6.47 (1.77, 23.61) ‡
PG present at time of procedure	3.31 (1.41, 7.76) ‡	4.58 (1.72, 12.22) ‡

*includes: cardiac catheterization, laparoscopy, arthroscopy, thoracoscopy, core needle biopsy, epidural or other small needle injection

†$p<0.05$; ‡$p<0.01$

Odds ratios from generalized linear mixed models with random intercepts for patients with multiple additional procedures, binomial distribution and logit link. Variables with $p<0.10$ from univariable analysis included.

Supplementary Table 1: Examples of procedures by category

Skin Biopsies	- Shave biopsy - Punch biopsy
Minimally Invasive Surgeries/Small Needle Injections	- Laparoscopy - Arthroscopy - Core-needle biopsy - Epidural injection - Percutaneous Endoscopic Gastrostomy (PEG)
Small Open Surgeries	- Thyroid surgery - Breast lumpectomy - Axillary lymphadenectomy - Fistulotomy and placement of seton - Carpal tunnel release/trigger finger release
Large Open Surgeries	- Exploratory laparotomy - Colectomy - Total knee/hip replacement - Ileostomy revisions/takedown - Below-the-knee/foot amputation
Mohs Surgery/Skin Excision/Debridement	- Mohs surgery - Skin excision - Wound debridement